The fate of patients with retinal artery occlusion and Hollenhorst plaque

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Objective: **Ocular symptoms and signs often herald hemispheric neurological events associated with extracranial cerebrovascular disease. However, the presence of a Hollenhorst plaque (HP) or retinal artery occlusion (RAO) and the risk of stroke is unclear. The purpose of this study was to review the outcomes of all patients who presented with a HP or RAO at a single institution.**

Methods: **Between 2000 and 2005, the management and outcome of 130 consecutive patients with a diagnosis of HP, central RAO, or branch RAO (ICD-9 codes 362.30 to 362.33) were reviewed. Patients with transient monocular visual loss (amaurosis fugax), retinal venous occlusion, and other ocular pathologies were excluded. Electronic and hardcopy medical records were reviewed for demographic data, clinical variables, radiological, and noninvasive vascular lab testing. Duplex and magnetic resonance angiography (MRA) of the carotid arteries were reviewed to confirm the presence of a lesion and quantify the degree of stenosis.**

Results: **During the study interval, 70 males and 60 females, with a mean age of 68 ± 16 (±SD) years underwent ophthalmologic evaluation. Symptoms were present in 61% of patients and included eye pain, blurred vision, or atypical visual symptoms, while 39% were asymptomatic. Atherosclerotic risk factors in this population included the presence of hypertension (73%), diabetes (33%), hyperlipidemia (75%), and tobacco use (38%). A majority of patients underwent carotid interrogation via Duplex imaging (68%). Carotid bifurcation stenoses ipsilateral to the ocular findings were <30% in 68% of the patients, between 30 and 60% in 22% and >60% in only 8% of patients. Six patients with lesions greater than 60% went on to have either a carotid endarterectomy or carotid stenting. Follow-up data on this group ranged from 1 to 49 months (median, 22 months), with no stroke or transient ischemic attack identified. There were five deaths during follow-up; none related to stroke. Serial carotid Duplex examinations failed to identify progression of carotid stenoses in this group of patients. Overall survival was 94% at 36 months for this cohort.**

Conclusion: **The presence of a HP or RAO is associated with a low prevalence of extracranial cerebrovascular disease that requires intervention. Furthermore, in contradistinction to amaurosis fugax, these ocular findings are not associated with a high risk for hemispheric neurological events. (J Vasc Surg 2007;46:1125-9.)**

Hollenhorst first described the embolization of cholesterol crystals to the retinal circulation in 1958.[1] Subsequent reports indicated that these retinal emboli were associated with carotid atherosclerosis, visual loss, and strokes.[2] Consequently, the identification of a Hollenhorst plaque (HP, Fig 1) or retinal artery occlusion (RAO) has led to concern for associated cerebrovascular disease and hemispheric neurological events.

Carotid endarterectomy (CEA) has been established by several large, prospective, randomized trials as a safe and effective intervention for reduction of stroke risk in symptomatic patients with significant carotid stenosis.[3,4] Currently, there is a paucity of data on the natural history of patients presenting with either HP or RAO. The dilemma remains whether to apply data from symptomatic carotid trials to the management of patients with these ocular findings. Our goal was to review the outcome of all patients who presented with the ocular findings of a HP or RAO and assess if these findings heralded future stroke.

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METHODS

After Institutional Review Board (IRB) approval, a retrospective review was performed of patients at the Cleveland Clinic Foundation with a diagnosis of HP, central RAO or branch RAO (ICD-9 codes 362.30 to 362.33). A total of 130 patients treated from 2000 to 2005 formed the basis for this study. The following diagnoses were excluded: transient monocular visual loss (amaurosis fugax, ICD-9 code 362.34), retinal venous occlusion (362.35 to 362.37), and other ocular conditions including optic neuropathy, retinopathy, and chronic ocular ischemia. Demographic data and risk factors were collected including age, smoking history, diabetes mellitus, hypertension, renal failure (serum Cr >3.0 mg/dL), and hyperlipidemia from electronic and hard copy medical records. Additional laboratory data, including hypercoagulable testing obtained in selected cases, were recorded. All radiological imaging and noninvasive vascular laboratory testing were reviewed. All duplex studies of the carotid arteries were reviewed via captured and stored electronic images (MagicView x-ray program) to confirm the presence of a lesion and quantify the degree of stenoses. Duplex examinations were performed in Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) accredited laboratories.

Fig 1. Hollenhorst plaque. Note the bright yellow cholesterol embolus lodged at the retinal artery bifurcation.

Carotid stenoses were defined using flow velocities and spectral analysis. Given the slightly different stratification reporting in the laboratories performing Duplex, patients were grouped as <30%, 30% to 60%, and >60% for simplicity. All clinical, perioperative, and demographic data were obtained through review of original hospital, and physician records including data collected prospectively in a departmental registry.

For statistical analyses, a *P* value of less than .05 was considered significant. Life table analyses were performed to calculate survival and stroke-free survival curves. Interval of follow-up at the Cleveland Clinic Foundation was recorded (median 22 months, range 1 to 49 months).

RESULTS

Patient demographic and clinical factors are displayed in Table I. Patients were considered to have hypertension, diabetes mellitus, hyperlipidemia, or coronary artery disease on patient history or treatment history for each disease process. Patients were considered to have renal failure if they had a serum creatinine greater than 3.0 mg/dL or were on chronic dialysis. Atherosclerotic risk factors in this population included the presence of hypertension (73%), diabetes (33%), hyperlipidemia (75%), coronary artery disease (59%), and tobacco use (38%). This represented a similar risk profile when compared with patients with extracranial cerebrovascular disease at our institution.[5] We found five patients in this cohort with hypercoagulable states; including two patients with lupus anticoagulant and two with anticardiolipin antibodies. Six patients (5%) carried a diagnosis of previous cerebrovascular accident. Furthermore, six patients carried the diagnosis of giant cell arteritis, and one patient had lupus. Lastly, there were five patients with documented patent foramen ovale or septal defect and four patients with atrial fibrillation (9/130 patients, 7%).

Table I. Demographics and clinical factors in patients presenting with retinal artery occlusion or Hollenohorst plaque

	N = 130	*%*
Mean age	68 ± 16 y	
Male	70	54%
Hypertension	95	73%
Diabetes	43	33%
Hyperlipidemia	98	75%
Coronary artery disease	77	59%
Tobacco use*	50	38%
Renal failure	0	0%
Hypercoagulable state	5	4%
Previous CVA	6	5%

CVA, Cerebrovascular accident.
*Both current and previous users.

During the study interval, 70 males and 60 females, with a mean age of 68 ± 16 (SD) years underwent ophthalmologic evaluation. In 80 patients (61%), evaluation was performed for eye pain, blurred vision, partial vision loss/field defect, or atypical visual symptoms. None of these patients had transient monocular blindness consistent with amaurosis fugax. Of the patients presenting with eye symptoms or visual complaints, 68 had unilateral symptoms vs 12 with bilateral symptoms. Of those with unilateral symptoms, there was a two to one preponderance of left sided vs right sided symptoms.

Fifty patients (39%) were asymptomatic and had no visual complaints. These individuals had RAO or HP diagnosed on fundoscopic examination. When looking at the retinal lesions of all 130 patients, there were 95 patients with HP (37 patients with retinal examinations performed at outside institutions), 34 patients with branch RAO, and one patient with central RAO. Again, there was a preponderance of left sided lesions. HP were found 48% of the time on the left, 41% on the right, and 11% bilaterally. The RAO were 47% left, 38% right, and 15% bilateral.

The vast majority of patients were referred to the vascular laboratory and underwent carotid interrogation via Duplex imaging (n = 88, 68%). Carotid bifurcation lesions ipsilateral to the ocular findings were <30% in 70% of the patients undergoing Duplex, between 30% and 60% in 22% and >60% in only 8% of patients (Table II). Six of the eight patients with lesions greater than 60% went on to have either a CEA (n = 4) or carotid stenting (n = 2). This group included four females and two males. All six patients had critical carotid artery stenosis (>80%) and underwent surgery or stenting without perioperative complications. The remaining two patients were managed medically for a moderate (60%) carotid stenosis in one patient and severe comorbidities precluding operative therapy in the other.

Echocardiographic studies were performed in approximately 20% of patients in order to identify a more proximal source of arterial embolization. Despite findings of minor

Table II. Carotid bifurcation stenoses by duplex ipsilateral to ocular findings

Stenosis %	*N = 98**	*%*
<30%	68	70%
30% to 60%	22	22%
>60%	8	8%

*98 carotid bifurcations in 88 patients; 10 patients with bilateral ocular findings.

valvular problems, no patient had a definitive cardiac or aortic arch source for the retinal findings and none underwent long-term anticoagulation. Also, aortic or carotid dissection was not found in any patient in this series.

Follow-up data ranged from 1 to 49 months (median 22 months). In this cohort, 71 patients (55%) had at least one follow-up carotid Duplex study performed within the first 3 months. Furthermore, 12% had two and 6% had three or more serial noninvasive examinations. Serial Duplex examinations failed to identify progression of carotid stenosis in this group of patients (mean Duplex interval, 9 months). In follow-up, no stroke or transient ischemic attack was identified in these 130 patients. There were five deaths; none related to stroke. Two patients died of cardiac disease; one after myocardial infarction and the other from congestive heart failure. Two patients succumbed to cancer (small cell-lung and ovarian). One patient died after complications from a hip fracture. Stroke-free survival and overall survival were equivalent at 94% at 3 years in this cohort (Fig 2).

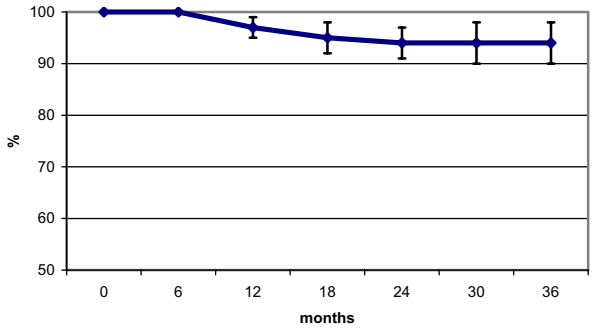

Fig 2. Overall survival rate. Overall survival was 94% at 36 months (SE <10%). There were five deaths during this interval, but none related to strokes. Patients at risk: time 0 = 130 patients; 12 months = 80 patients; 24 months = 58 patients; and 36 months = 32 patients.

DISCUSSION

Vascular surgeons often see patients presenting with eye symptoms with a concern for extracranial carotid occlusive disease. Implicit in the referral of these patients is that an arterial embolus from the carotid bifurcation is leading to embolic ischemic damage to the eye, and that this may be a harbinger of future ipsilateral hemispheric events. The eye symptoms generally fall into the four categories of transient monocular visual loss (TMVL, ie, amaurosis fugax), chronic ocular ischemia, RAO, and HP. The latter two are the subject of this article.

The treatment of patients with symptomatic severe carotid atherosclerosis has been documented. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), patients with TMVL, transient ischemic attack or nondisabling stroke, and severe carotid bifurcation stenosis were randomized to either CEA or medical management.[3] Surgical management led to a 2-year ipsilateral stroke rate of 9% vs 26% for patients undergoing medical management alone ($P < .001$). However, subsequent analyses showed the rate of stroke to be less in patients presenting with TMVL vs hemispheric ischemia.[6] Still, patients presenting with TMVL have a 17% 2-year stroke rate and a 1% to 2% yearly rate of permanent blindness secondary to retinal stroke.[7] Chronic ocular ischemia is another well-described entity in which retinal metabolic demand is not met by the blood supply leading to visual deterioration. Despite being much less common an entity than TMVL, surgical management of carotid occlusive disease in the setting of chronic ocular ischemia has led to gratifying improvement in visual function.[8,9]

Hollenhorst's description of bright plaques in the retina implicated cholesterol crystal embolization from ulcerated proximal atherosclerotic lesions.[2] Further data linking HP to critical carotid stenosis was described by Chawluk and colleagues.[10] Patients with HP were more likely to have a stenotic or ulcerated carotid plaque than patients with TMVL ($P = .04$). Kirshner et al reviewed 131 cases of cerebrovascular disease with ocular manifestations that underwent CEA.[11] Visual symptoms were mostly in the form of TMVL. However, in 20 patients, permanent visual loss was secondary to RAO. Despite correction of the ipsilateral carotid stenosis, patients presenting with permanent visual loss had no restoration of visual function. Five cases of permanent visual loss secondary to RAO were preceded by multiple episodes of TMVL. These reports taken together suggested that cholesterol emboli to the eye are herald signs of embolizing carotid bifurcation atheroma and further ipsilateral hemispheric neurological damage may ensue.

Over time, this view has undergone modification. Bunt studied 60 patients with visual symptoms and evaluated all with cerebral angiography.[12] Of the 60 patients, 18 patients had asymptomatic HP found on ocular examination. Half of these patients had ipsilateral carotid bifurcation disease, but only five of the 18 required CEA. None of the patients presenting with HP developed cerebral symptoms. In contradistinction, 26 patients with amaurosis fugax had a 70% incidence of carotid bifurcation disease with 50% requiring CEA. Bunt concluded that HP alone was a poor predictor of future embolic events to either the retina or the carotid circulation.[12] Of interest, sequential fundoscopic examination found persistence of HP in five of nine patients for over a year. This indicated that the incidental finding of HP could represent an embolic event from long ago. Sim-

ilarly, Schwarcz et al studied 64 patients with HP in which 28 patients underwent CEA for corresponding ipsilateral carotid stenosis.[13] Despite correction of stenoses, four patients developed new ipsilateral HP and two late strokes occurred. They concluded that CEA in patients with asymptomatic HP did not prevent the development of new HP or late cerebrovascular events.

McCullough et al examined 105 patients presenting with TMVL (26%), and HP (19%), while the majority of patients (55%) had other symptoms including anterior ischemic optic neuropathy, optic atrophy, and venous occlusion.[14] The finding of a positive carotid scan (>50% to 60% stenosis) was low for both TMVL (20%) and HP (18%) with poor predictive value. All other ocular findings, except venous stasis retinopathy, had no predictive value in identifying carotid occlusive disease. They concluded that ocular symptoms and findings at fundoscopic examination were generally poor predictors of significant carotid disease. Similarly, Wakefield and colleagues reviewed patients with visual disturbances who had duplex examination performed from June 1996 to December 2001.[15] Patients (n = 98) had Duplex secondary to TMVL, HP, and RAO. Similar to our results, only a small percentage of patients with HP (2/36 carotid arteries), or RAO (2/18 carotid arteries) had significant occlusive disease warranting CEA. These authors concluded the patient who presented with visual signs or symptoms may need to undergo a screening carotid duplex examination (as a small percentage will have a surgically correctable disease), but if the screening examination was normal then a follow-up duplex imaging was not required.

Recent evidence indicates different mechanisms for symptomatic vs asymptomatic retinal emboli. The former are associated with ipsilateral carotid stenosis and middle cerebral artery microembolic signals documented by transcranial Doppler.[16,17] Thus, TMVL may indicate a recent ischemic event to the eye due to an embolic event from the carotid bifurcation to the ophthalmic artery with a well documented risk of future hemispheric or retinal stroke. On the other hand, HP and RAO are often asymptomatic lesions of unknown chronicity found on ocular examinations and may represent a long standing prior event of a small cholesterol embolus from any proximal source.

Limitations of our study include the retrospective nature of the study. These patients were seen at a tertiary referral hospital. Thus, other patients with ocular findings and severe carotid pathology may have been treated at their local centers without referral leading to a bias. The diagnostic testing and management of these patients was not dictated and, thus, not uniform. Many patients were initially evaluated by their primary care doctor and referred to an ophthalmologist. Only a minority were seen by a vascular surgeon. Lastly, there was inconsistent follow-up in this patient population, which could have affected the long-term results. The lack of carotid stenosis progression is based on limited Duplex examinations and follow-up and requires further confirmation. Despite these limitations, this series represents the largest study of the natural history of retinal arterial branch occlusions and Hollenhorst plaques that we are aware of. Furthermore, the identification of 130 patients from hospital diagnoses codes rather than solely from referrals to the Department of Vascular Surgery or departmental registries adds to the validity of this study.

The impetus for our study was the prevailing notion among both referring physicians and consulting surgeons in our area that HP or RAO represented a vascular surgical emergency. Apparently, variable management algorithms for patients with this process seem widespread.[18] Based on our data, we conclude the presence of a HP or RAO is associated with a low prevalence of extracranial cerebrovascular disease that requires intervention. Furthermore, these ocular findings, in the absence of carotid stenosis, are not associated with a high risk for hemispheric neurological events and represent a fairly innocuous event in contradistinction to amaurosis fugax. Carotid artery therapy may be needed but can be based on variables independent of the ocular findings. Frequently, the decision to proceed with surgical therapy will rest on the degree of carotid stenosis, other neurological symptoms and comorbidities independent of the ocular findings.

AUTHOR CONTRIBUTIONS

Conception and design: VK, AD, GS
Analysis and interpretation: VK, AD, GK
Data collection: AD
Writing the article: AD, VK
Critical revision of the article: GK
Final approval of the article: VK, AD, GK
Statistical analysis: VK, AD
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Overall responsibility: VK

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